Does Hepatic Steatosis Influence the Virological Response with Chronic Hepatitis B Patients Treated with Entecavir or Tenofovir Disoproxil Fumarate?

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ABSTRACT

Background: *The effect of hepatic steatosis on the response to antiviral therapy administered in chronic hepatitis B patients is yet to be clarified. In this study, our aim was to determine the effect of hepatic steatosis on the virological response in chronic hepatitis B patients who were treated with entecavir or tenofovir disoproxil fumarate.*

Methods: *This retrospective cohort study was performed using the data of liver biopsy-proven chronic hepatitis B patients with or without hepatic steatosis, who received entecavir or tenofovir disoproxil fumarate treatment between 2012 and 2017. The undetectable serum hepatitis B virus deoxyribonucleic acid level under treatment was defined as the complete virological response. The predictors of virological response were determined, and it was checked whether the virological response was affected by hepatic steatosis in chronic hepatitis B patients who have undergone entecavir or tenofovir disoproxil fumarate treatment.*

Results: *A total of 324 chronic hepatitis B patients, of which 203 (63%) were males, were included in the study. The median age of the patients was 42 years (range: 35-51 years). Hepatic steatosis was observed in 25% of the patients, and steatohepatitis in 4%. The median time to complete virological response was found to be 6 months (range: 3-9 months). In the full analysis model, the log hepatitis B virus deoxyribonucleic acid was determined as the factor most associated with virological response ($P < .001$). No statistically significant relationship was detected between hepatic steatosis and virological response ($P = .409$).*

Conclusion: *Concomitant hepatic steatosis has no significant impact on the virological response in chronic hepatitis B patients who have undergone entecavir or tenofovir disoproxil fumarate treatment.*

Keywords: *Chronic hepatitis B, hepatic steatosis, virological response*

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) together with socioeconomic development and dietary changes are seen at increasing rates. The worldwide prevalence of NAFLD in the adult population has been reported to be approximately 25%.[1-3] Hepatic steatosis is defined histologically as hepatic fat content of ≥5% of liver weight. The most significant characteristic in the liver disease progression is the transformation of steatosis to steatohepatitis. In steatohepatitis, ballooning and inflammation accompany steatosis.[1,4,5]

Hepatitis B virus (HBV) and NAFLD are the 2 major reasons for chronic liver disease. An increase in the number of chronic hepatitis B (CHB) patients with concomitant hepatic steatosis is inevitable when considering the increase in NAFLD.[6] Chronic hepatitis B and NAFLD may also cause liver cirrhosis, and they have a complex pathogenesis.[2] The association of NAFLD and CHB can potentially speed up the progression of liver cirrhosis. Treatment strategies for NAFLD now include modification in lifestyle, surgical interventions for weight loss, and pharmacotherapy. However, an effective and optimal therapy in all patients has not been established yet.[7] This increases the importance of the virological response in CHB patients especially with concomitant hepatic steatosis.

In several studies, chronic HBV infection was found to be associated with hepatic steatosis.[6,8,9] In contrast, several other studies have reported that the probability of

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observing hepatic steatosis in patients with chronic HBV infection is similar to that of the normal population, and the reason behind fattiness in these patients is linked to metabolic causes rather than HBV.[10-14]

Entecavir (ETV) and tenofovir disoproxil fumarate (TDF) are extremely effective drugs with high genetic barriers. Both drugs are often used to treat CHB patients.[5] Although many studies have been performed to examine the relationship between chronic HBV infection and NAFLD, few have investigated whether hepatic steatosis affects the virological response in CHB patients who receive antiviral treatment.

Therefore, in this study, our aim was to investigate the effect of hepatic steatosis on the virological response of CHB patients treated with ETV or TDF and to determine the predictors of the virological response.

MATERIALS AND METHODS

Study Design and Patients

Our retrospective cohort study was performed at a single center and included patients diagnosed with CHB at the Ümraniye Teaching and Research Hospital between 2012 and 2017.

The CHB diagnosis was confirmed if the patient had serum hepatitis B surface antigen (HBsAg) positivity (at least 6 months), a serum HBV deoxyribonucleic acid (HBV-DNA) level >2000 IU/mL (at least 6 months), elevated or normal alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) levels, and liver biopsy results consistent with chronic HBV infection.[15]

Patients who were aged >18 years, who were diagnosed with biopsy-proven CHB (at least 6 portal tracts included in liver histopathology), and CHB patients who had been diagnosed with CHB but were about to receive their first treatment with ETV or TDF were included in the study.

Patients who had current or previous alcohol consumption ≥30 g/day for men and ≥20 g/day for women, a history of drugs use that may cause fatty liver (corticosteroids, diltiazem, valproic acid, etc.), other chronic liver diseases (autoimmune hepatitis, primary biliary cholangitis, drug-induced liver injury, hemochromatosis, Wilson disease, etc.), or other viral hepatitis agents with coinfections (hepatitis C, delta hepatitis, etc.) were excluded, as well as CHB patients who had not undergone biopsy or had less than 6 portal tracts on liver histopathology examination.

A total of 421 patients were initially identified. Those patients were diagnosed with CHB and met the inclusion criteria. The data of these patients were retrospectively recorded from the hepatology outpatient clinic follow-up files and the hospital database. After applying the exclusion criteria, a total of 357 patients remained, and following further exclusion of those who did not show up for regular follow-ups, did not comply with the treatment, or had incomplete data, the study included 324 patients for data analysis.

Approval for the study was received from the Ethics Committee of Ümraniye Teaching and Research Hospital where the study was performed. The study was performed in accordance with the Declaration of Helsinki.

Laboratory Data

Blood samples were taken in the morning after a fasting period of 8 hours. Before performing the liver biopsy, the laboratory data for ALT, AST, alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), albumin, fasting glucose, total bilirubin, total cholesterol, triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), HBsAg, hepatitis B e antigen (HBeAg), anti-HBe, and HBV-DNA levels of all patients were recorded. The ALT, AST, and HBV-DNA values were also recorded on the 1st, 3rd, 6th, 9th, and 12th months after treatment and every 6 months thereafter. The serum HBV-DNA levels were measured using the real-time polymerase chain reaction (PCR) method.

Virological Response

The undetectable serum HBV-DNA level under treatment was considered as a complete virological response (CVR).

Histopathological Evaluation

Patients were diagnosed with NAFLD and CHB according to the liver biopsy results. The biopsy specimens were fixed in 10% buffered formalin and were then embedded in paraffin blocks. The pathology slides were retrieved from the archives and were analyzed again by an experienced pathologist blinded to the laboratory results. The classification of the Histology Activity Index (HAI) and fibrosis (F) in the biopsy specimens was done according to the Ishak scoring system.[16] A score of F 3-6 was considered as significant fibrosis, a score of F 4-6 as advanced fibrosis, and a score of F 5-6 as cirrhosis. The evaluation of the hepatocytes in all tissue samples was made as the percentage of hepatocytes affected by fat droplets in content. The histological diagnosis of NAFLD was

accepted as the presence of ≥5% steatotic hepatocytes in a liver tissue section. In the diagnosis of non-alcoholic steatohepatitis (NASH) and evaluation of disease activity, the NASH CRN Network (Kleiner) classification was used. Throughout the whole tissue specimen, the percentage of hepatocytes containing fat droplets was assessed and classified as Grade 0 (<5%): none, Grade 1 (5-33%): mild, Grade 2 (>33-66%): moderate, and Grade 3 (>66%): severe.[17]

Statistical Analysis

Data obtained in the study were analyzed with the R Software v.3.5.1 (R statistical software; Institute for Statistics and Mathematics, Vienna, Austria) using the rms, mgcv, and ggplot2 packages. Continuous variables were presented as median and interquartile values, and categorical variables as number (n) and percentage (%).

The primary outcome was virological response (VR), defined as the time to undetectable HBV-DNA (months) within 48 weeks of starting the ETV or TDF treatment.

Two primary models were evaluated in this study; the first model (full model) included 20 predictor variables of age, sex, albumin, ALT, AST, ALP, GGT, total bilirubin, TG, HDL-C, LDL-C, fasting glucose, diabetes mellitus (DM), HAI, fibrosis, hepatic steatosis, NASH, treatment (ETV or TDF), HBeAg, and log HBV-DNA. Variables with very low or very high frequency were excluded. To decrease the complexity of the full model and to provide a smaller model that would be more practical for bedside use, variables were selected using the backward-stepwise approach with an alpha criterion of 0.25. Variables with very low (<5%) or very high frequency (>95%), and variables with >50% missing data were not included in the model. It was calculated that the sample size needed to be at least 184 in order to estimate the entire distribution of CVR with a global margin of error not exceeding 0.1.

The proportional odds logistic regression method was utilized in examining the relationship between the primary outcome VR and the potential predictors.[18]

The effects of individual predictors of CVR were reported using the regression coefficient and 95% CI. Age, albumin, ALT, AST, ALP, GGT, total bilirubin, TG, HDL, LDL, fasting glucose, and log HBV-DNA were included in the model as flexible smooth parameters using a restricted cubic spline. The effects of continuous predictors were summarized using the interquartile range values. Due to the expected interaction between log HBV-DNA and HBeAg, "log HBV-DNA × HBeAg; fasting glucose × DM" interaction terms were added to the regression model. The relative importance of each predictor in the models was estimated with a partial chi-square value for each predictor divided by the total chi-square value of the model to estimate the independent contribution of the predictor to the variance of the outcome. The comparison between the models was made with an assessment of fit (likelihood ratio chi-square), quality (Akaike and Bayesian information criteria (AIC and BIC)), and predictive accuracy (Somers' rank and *Dxy*) and R^2.

The variables that were not normally distributed between the 2 groups (fibrosis and HBV-DNA) were compared using the Mann–Whitney *U* test, while the variables that were not normally distributed among the 3 groups (fibrosis and HBV-DNA) were compared using the Kruskal–Wallis test.

RESULTS

A total of 324 patients, 203 males (63%) and 121 females (37%), were included in the study. The median age of the patients was 42 years (range: 35-51 years). Diabetes mellitus was detected in 33 patients (10%), arterial hypertension in 29 (9%), and hyperlipidemia in 17 (5%). The median log HBV-DNA was found as 12.3 (range: 9.2-15.7). Hepatitis B e antigen positivity was determined in 64 patients (20%). Hepatic steatosis was determined in 82 (25%) patients. Sixty-eight (21%) were mild (Grade 1) and 14 (4%) were moderate (Grade 2). Non-alcoholic steatohepatitis was determined in 13 patients (4%). The median HAI score was 6 (range: 5-8). Entecavir treatment was applied to 90 patients (28%) and TDF to 234 (72%). Table 1 demonstrates patients' clinical characteristics and laboratory data.

In treatment-naive patients, the median log HBV-DNA value was 12.5 (range: 9.5-15) in patients with hepatic steatosis and 12.4 (range: 9.2-15.9) in patients without hepatic steatosis. There was no statistically significant difference between the 2 groups ($P = .838$). In treatment-naive patients, the median log HBV-DNA value was 12.4 (range: 9.2-15.9) in patients with no hepatic steatosis, 12.5 (range: 9.5-15) in patients with mild hepatic steatosis, and 11.5 (range: 9.3-15.1) in patients with moderate hepatic steatosis. No statistically significant difference was observed among these groups ($P = .837$).

Table 1. Baseline Demographic, Clinical Characteristics, and Laboratory Data of the Study Patients

Sex (male)	63% (203)
Age (year)	42 (35-51)
Diabetes mellitus	10% (33)
Hypertension	9% (29)
Hyperlipidemia	5% (17)
Albumin (mg/dL)	4.3 (4.1-4.5)
ALT (U/L)	40 (23.75-75.25)
AST (U/L)	30 (22-48)
ALP (U/L)	75 (62-91)
GGT (U/L)	24 (17-39)
Total bilirubin (mg/dL)	0.70 (0.51-0.96)
Fasting glucose (mg/dL)	93 (86-101)
Triglyceride (mg/dL)	92 (71-131)
Total cholesterol (mg/dL)	182 (160.25-204.75)
LDL-C (mg/dL)	119.5 (98.25-139)
HDL-C (mg/dL)	44 (36-51)
HbeAg (positive)	20% (64)
HBV-DNA (log_{10} IU/mL)	12.3 (9.2-15.7)
Timing of undetectable HBV-DNA (month)	6 (3-9)
NASH	4% (13)
HAI	6 (5-8)
Treatment	
ETV	28% (90)
TDF	72% (234)
Fibrosis	
0-1	5%(15)
2	41% (132)
3	32% (105)
4	14% (44)
5	6% (20)
6	2% (8)
Steatosis	
0	75%(242)
1	21%(68)
2	4%(14)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; GGT, gamma-glutamyl transferase; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; HbeAg, hepatitis B e antigen; HBV-DNA, hepatitis B virus deoxyribonucleic acid; NASH, non-alcoholic steatohepatitis; HAI, histological activity index; ETV, entecavir; TDF, tenofovir disoproxil fumarate.

In treatment-naive patients, the median fibrosis score was 3 (range: 2-3) in patients with hepatic steatosis and without hepatic steatosis, showing no statistically significant difference between the groups (P = .511). In treatment-naive patients, the median fibrosis score was 3 (range: 2-3) in patients without hepatic steatosis, 3 (range: 2-3) in patients with mild hepatic steatosis, and 3 (range: 2-4) in patients with moderate hepatic steatosis, again demonstrating no statistically significant difference among these groups (P = .406). The median fibrosis score was 4 (range: 3-5) in patients with NASH and 3 (range: 2-3) in those without NASH. The fibrosis score in the NASH group was statistically significantly higher (P = .007).

In treatment-naive patients, the prevalence of significant fibrosis was 53.6% (44/82) in patients with hepatic steatosis, while it was 54.9% (133/242) in patients without hepatic steatosis, with no statistically significant difference between the 2 groups (P = .838). In treatment-naive patients, the prevalence of advanced fibrosis was 24.4% (20/82) in patients with hepatic steatosis and 21.4% (52/242) in patients without hepatic steatosis. Again, no statistically significant difference was detected between the 2 groups (P = .585). In treatment-naive patients, the prevalence of cirrhosis was 13.4% (11/82) in patients with hepatic steatosis, whereas it was 7% (17/242) in patients without hepatic steatosis. Once again, no statistically significant difference between the 2 groups could be established (P = .075).

The median time to CVR (undetectable HBV-DNA) was found to be 6 months (range: 3-9 months). Figure 1 shows the frequency distribution of the time to CVR.

In the full model, log HBV-DNA (regression coefficient: 2.053, 95% CI: 1.258-2.849; $P < .001$) was determined to be the factor most associated with CVR. Hepatitis B e antigen (regression coefficient: 2.747, 95% CI: 1.371-4.123; $P < .001$), ETV treatment (regression coefficient: 1.291, 95% CI: 0.649-1.933; $P < .001$), total bilirubin, and fasting glucose were other factors significantly associated with VR. No statistically significant relationship was determined between VR and hepatic steatosis (P = .409) and fibrosis (P = .197) (Table 2).

The partial effect log HBV-DNA is summarized in Figure 2. Delayed CVR was more evident when log HBV-DNA was >10 (Figure 2).

The relative impact of all predictors in the model is summarized in Figure 3. Log HBV-DNA, HBeAg, ETV treatment,

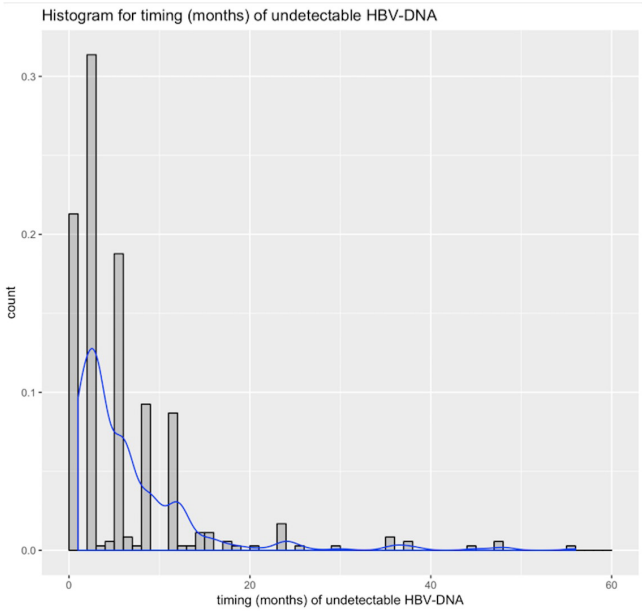

Figure 1. The frequency distribution of timing (months) of undetectable HBV-DNA (virological response). HBV-DNA, hepatitis B virus deoxyribonucleic acid.

total bilirubin, and fasting glucose were statistically determined to be the factors with the most effect on CVR. Log HBV-DNA was ranked as the strongest predictor for decline in VR. Following the backward-stepwise variable selection, log HBV-DNA, HBeAg, the use of ETV, and ALT remained in the model (reduced model). Differences in model fit, quality, and predictive accuracy were considered negligible and comparable (Table 3).

A nomogram was also developed using the reduced model and variable coefficient in estimating the probability of the timing of CVR (in months) (Figure 4).

DISCUSSION

With the worldwide increase in NAFLD, a concomitant increase in CHB and NAFLD is inevitable. The prevalence of NAFLD has been reported to vary between 6% and 35% worldwide,[19] while the prevalence of hepatic steatosis in CHB patients has been reported to vary between 14% and 51%.[6,8-10,20] In the current study, hepatic steatosis was seen in 25% of the CHB patients, a finding consistent with those from prior studies.

Some studies have suggested that the prevalence of hepatic steatosis is higher in CHB patients when compared to the general population.[6,8,9] The HBV X protein has been associated with the increased fatty liver disease in CHB patients. Wu et al[21] showed that the HBV X protein upregulates the liver fatty acid binding protein 1 in the liver and thus causes lipid accumulation.[21] In a multicenter study of 1069 cases in Turkey,[20] the prevalence of hepatosteatosis in CHB patients was reported as 42.2%. The rate may have been high since ultrasound was used in the diagnosis of hepatosteatosis in that study. The reason for this rate being higher than that in our study

Table 2. Adjusted Regression Coefficient and SE for Individual Predictors of Timing (Months) of Undetectable HBV-DNA (Virological Response) Included in the Full Model

	Regression Coefficient (95% CI)	*P*
Fibrosis (from 2 to 3)	0.219 (−0.113 to 0.552)	.197
HAİ (from 5 to 8)	−0.077 (−0.562 to 0.408)	.755
Treatment (ETV)	1.291 (0.649 to 1.933)	**<.001**
Sex (male)	−0.190 (0.645 to −2.455)	.065
Age (from 35 to 51)	0.142 (−0.272 to 0.556)	.651
HbeAg (Positivity)	2.747 (1.371 to 4.123)	**<.001**
Log_HBV-DNA (from 9.25 to 15.70)	2.053 (1.258 to 2.849)	**<.001**
ALT (from 23.75 to 75.25)	0.396 (−0.757 to 1.551)	.186
AST (from 22 to 48)	0.545 (−0.608 to 1.700)	.629
TG (from 71 to 131)	0.134 (−0.400 to 0.669)	.852
LDL-C (from 98.25 to 139)	−0.198 (−0.651 to 0.253)	.379
HDL-C (from 36 to 51)	0.338 (−0.123 to 0.799)	.104
ALP (from 62 to 91)	0.438 (0.003 to 0.872)	.118
GGT (from 17 to 39)	0.006 (−0.656 to 0.670)	.432
Albumin (from 4.1 to 4.5)	−0.036 (−0.303 to 0.230)	.913
Fasting Glucose (from 86 to 101)	−0.169 (−0.496 to 0.157)	**.050**
DM (yes)	−0.514 (−1.786 to 0.757)	.231
Total bilirubin (from 0.51 to 0.96)	−**0**.072 (−0.524 to 0.380)	**.034**
NASH (yes)	1.143 (−0.474 to 2.760)	.165
Steatosis (no, Grade 0)	Reference	.409
Steatosis (mild, Grade 1)	0.412 (−0.286 to 1.112)	
Steatosis (mode, Grade 2)	−0.244 (−1.902 to 1.413)	

ALT, alanine aminotransferase (U/L); AST, aspartate aminotransferase (U/L); ALP, alkaline phosphatase (U/L); GGT, gamma-glutamyl transferase (U/L); TG, triglyceride (mg/dL); LDL-C, low-density lipoprotein cholesterol (mg/dL); HDL-C, high-density lipoprotein cholesterol (mg/dL); HbeAg, hepatitis B e antigen; HBV-DNA, hepatitis B virus deoxyribonucleic acid; NASH, non-alcoholic steatohepatitis; HAI, Histological Activity Index; ETV, entecavir; TDF, tenofovir disoproxil fumarate; DM, diabetes mellitus; NASH, non-alcoholic steatohepatitis. Bold values were significant factors associated with virological response.

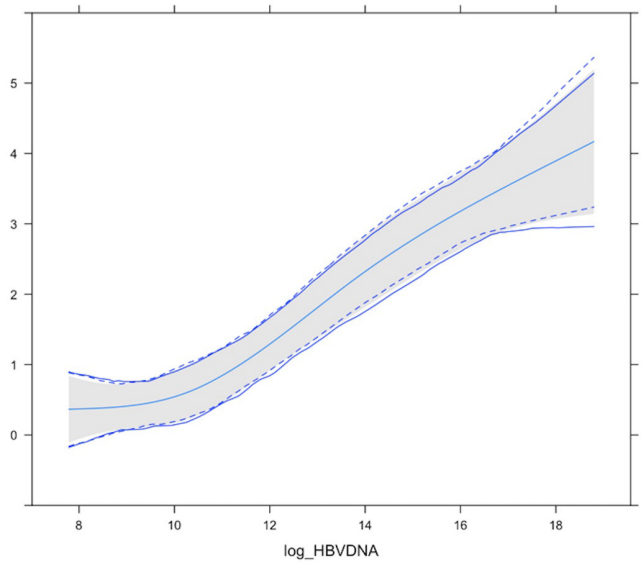

Figure 2. Partial effect plot of log_HBV-DNA. Interaction between virological responses with log_HBV-DNA. HBV-DNA, hepatitis B virus deoxyribonucleic acid.

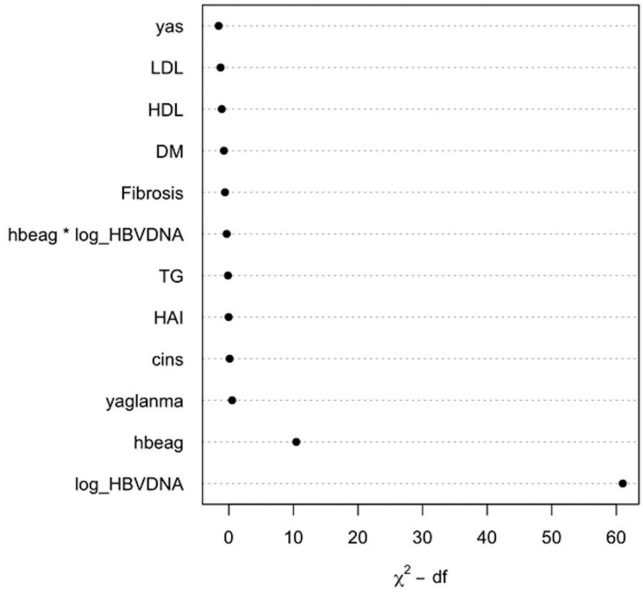

Figure 3. Importance of individual predictors. The importance of each predictor in the full model was calculated as the proportion of explainable outcome variation contributed by each predictor (partial chi-square value for each predictor divided by the model's total chi-square). ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; GGT, gamma-glutamyl transferase; LDL, low-density lipoprotein cholesterol; HDL, high-density lipoprotein cholesterol; HBeAg, hepatitis B e antigen; HBV-DNA, hepatitis B virus deoxyribonucleic acid; NASH, non-alcoholic steatohepatitis; HAI, Histological Activity Index (treatment; ETV, entecavir; TDF, tenofovir disoproxil fumarate); DM, diabetes mellitus.

Table 3. Model Performance of Both Full and Reduced Models

Model	*df*	LR X^2	R^2	Rho	AIC	BIC
Full model	37	188	0.572	0.731	806	1063
Reduced model*	12	214	0.496	0.681	1179	1310

*Log HBV-DNA × HbeAg interaction term was added.
AIC, Akaike information criteria; BIC, Bayesian information criteria; HbeAg, hepatitis B e antigen; LR: Likelihood Rations.

could be due to the fact that the hepatic steatosis diagnosis in the CHB patients of the current study was made histopathologically.

In contrast, several reports in the literature have shown similar prevalences of hepatic steatosis in the general population and in CHB patients, which are in accordance with our findings.[11-14] Thomopoulos et al[22] and Chen et al[23] reported the frequency of NAFLD in biopsy-proven patients with CHB to be 18% and 18.69%, respectively.[22,23] In a meta-analysis that included 17 studies, the overall prevalence of hepatic steatosis was 29.6%.[13] In parallel with this, several studies have reported that hepatic steatosis in CHB patients does not occur because of virological factors but develops associated with host-related risk factors.[9,10,24-26] The above-mentioned results suggest that HBV has minimal effect on hepatic steatosis.

It has been reported that the HBV-DNA levels are lower in CHB patients with concomitant NAFLD when compared to those without NAFLD.[13] A study by Zhang et al[14] has shown that the serum HBV-DNA, HBsAg, and HBeAg levels are decreased during the development of NAFLD in CHB patients. Contrary to this, in our study, there was no significant difference in terms of median log HBV DNA values between the treatment-naive patients with and without hepatic steatosis (P = .838). Although the median log HBVDNA levels were found to decrease as the severity of steatosis increased in patients with hepatic steatosis, this decrease was not statistically significant (P = .837). There was no linear trend or stepwise relationship between steatosis severity and the HBV-DNA level. However, in the current study, an elevated log HBV-DNA and HBeAg positivity were determined to be the parameters most associated with a delay in VR. Elevated log HBV-DNA was also the parameter with the most significant effect on VR in our study. In addition, delayed CVR was more prominent when log HBV-DNA was >10. When the VR is delayed, an increase in the possibility of developing liver cirrhosis and hepatocellular carcinoma can be predicted as HBV-related necroinflammation has continued.

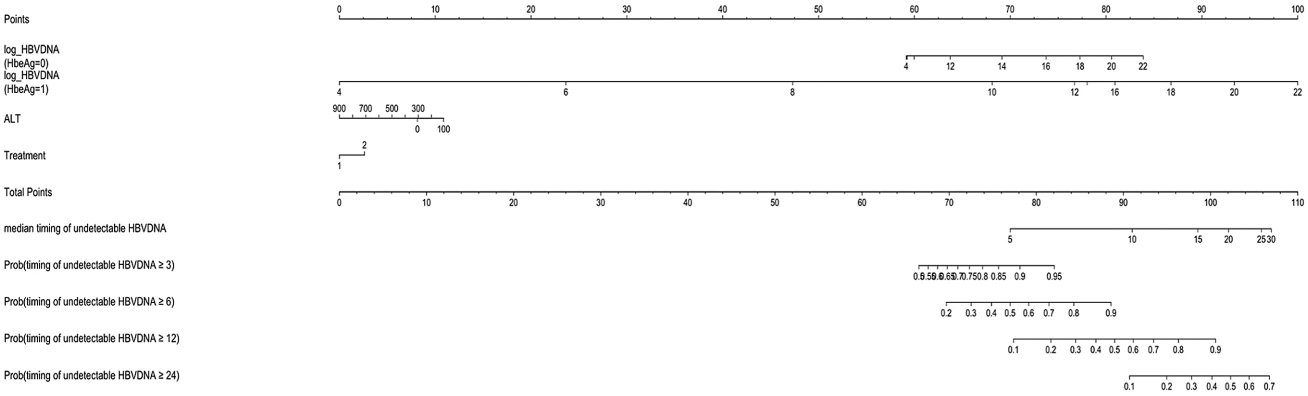

Figure 4. Nomogram for estimating the probability of CVR at follow-up. Treatment 1, tenofovir disoproxil fumarate; treatment 2, entecavir; ALT, alanine aminotransferase; CVR, complete virological response.

When the literature was examined about how the presence of NAFLD in CHB patients affects the VR, we saw that the issue has not been fully clarified. In a meta-analysis of 8 prospective cohort studies, 399 CHB patients with hepatosteatosis and 688 CHB patients without hepatosteatosis were examined, and it was reported that especially when the diagnosis was made using ultrasound and the treatment was applied with nucleotide analogs, hepatosteatosis in CHB patients was associated with a decrease in response to antiviral treatment. Jin et al[25] studied 267 patients diagnosed with CHB and treated with ETV and reported that the VR was lower in the group with NAFLD at the 24th, 48th, and 96th weeks.

It has been suggested that this situation could be due to a reduction in the bioavailability of antiviral drugs in hepatocytes with high fat content and the impact of cytochrome enzyme levels on the drug metabolism.[27,28] However, in a study by Ceylan et al[24] the serum level of HBV-DNA was reported to be lower in CHB patients in the presence of NAFLD and that hepatic steatosis had no effect on VR at the 6th and 12th months. A study of CHB patients that investigated the effect of hepatic steatosis on the response to treatment with nucleotide analogs demonstrated that hepatic steatosis had no significant effect, whereas there was a significant difference with respect to HBeAg seroconversion in the long-term follow-up period.[29] In another multicenter study, the long-term VR in CHB patients who underwent ETV and TDF treatment were reported not to be affected by the presence of hepatosteatosis.[20]

The abovementioned variable results from different studies could be due to the conduction of studies in different geographic regions and the use of different diagnostic methods in the determination of hepatic steatosis. The findings of our study support the view that hepatic steatosis has no significant effect on the VR. Moreover, the data also demonstrate that ETV may be associated with a late VR compared to TDF.

In a notable study of Li et al. it was reported that concomitant NAFLD in CHB patients had no effect on the long-term CVR, a finding in parallel with our study. In a recently study of Li et al[30] it was reported that concomitant NAFLD in CHB patients had no effect on the long-term CVR, a finding in parallel with our study.

In a meta-analysis, it was demonstrated that fibrosis staging was no different between CHB patients with or without histological hepatic steatosis.[13] In our study, the stages of fibrosis in patients with and without hepatic steatosis were similar (P = .511). There was no statistically significant difference in terms of median fibrosis values as the severity of hepatic steatosis increased (P = .406). In addition, the results of our study also could not detect a significant relationship between fibrosis and CVR. In their study conducted with a high number of patients, Li et al[31] reported that the presence of fatty liver in CHB patients was associated with a lower cirrhosis prevalence. In our study, there were no statistically significant differences among the rates of significant fibrosis, advanced fibrosis, and cirrhosis in treatment-naive patients with and without hepatic steatosis. On the other hand, in the presence of NASH, the fibrosis values were statistically higher (P = .007). The relatively small number of our NASH patients may have caused the discrepancy with the results from previous studies. Future prospective studies with larger cohorts may help to shed more light on this issue.

Using the data of log HBV-DNA, HBeAg, treatment (ETV or TDF), and ALT, a nomogram was developed in the current study in order to estimate the median time to an undetectable HBV-DNA level. The VR obtained after 3, 6, 12, and 24 months could be determined as an estimated percentage in the nomogram. As an example, in a patient with HBeAg positivity, the ALT level was 100 IU/mL, the log HBV-DNA was measured as 10, and the patient was given TDF treatment. According to the nomogram for this patient, the probability of median CVR was 6 months, and the probability for the timing of undetectable HBV-DNA ≥3 months was >90%.

Our study had some limitations. First, it had a retrospective design; thus, the originally unavailable body mass index, waist circumference, and HBV genotype data could not be included in the study. However, in a previous study conducted on a high number of patients in our region, genotype D was detected in 99.1% of the HBV infections.[32] We estimate that the majority of the HBV genotype in our patients with CHB is D. Second, most of our patients were from the same region, which limited the generalization of our results on a global scale. Third, we could not provide information on HBsAg clearance in this study due to the short follow-up time. Finally, we could not investigate the effect of hepatic steatosis on the VR since our study was designed to investigate the effect of hepatic steatosis on the biochemical response.

Also, the results of this study showed that the variables most strongly associated with VR were log HBV-DNA and HBeAg. Finally, we found that hepatic steatosis did not affect the treatment outcomes in CHB patients who underwent ETV or TDF treatment.

In conclusion, our results support the argument that hepatic steatosis do not affect the CVR in CHB patients treated with ETV or TDF.

Ethics Committee Approval: Ethics committee approval was obtained from Umraniye Teaching and Research Hospital (decision no: B.10.1.TKH.4.34.H.GP.0.01/176).

Informed Consent: Informed consent couldn't obtained due to the retrospective nature of this study.

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